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Seroepidemiology of Hantaan Virus Infection in Taiwan

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In order to investigate the infection rate of Hantaan virus in Taiwan, a total of 6,536 human serum samples were collected from residents, selected by stratified random sampling, from 19 townships covering four different ethnic groups: Aborigines, Fukien Taiwanese, Hakka Taiwanese, and Mainland Chinese. Serum samples were screened for Hantaan virus antibodies by indirect immunofluorescence. The prototype Hantaan virus (76/118)-infected Vero E6 cells were used as the viral antigen for the antibody detection. Among 6,536 human serum samples, 403 (6.2%) samples had Hantaan virus antibodies. The seropositive rates for males and females were 6.1% and 6.2%, respectively. A higher seropositive rate was found among Aborigines on the Orchid Islets (11.5%) and Fukien Taiwanese on the Penghu Islets (11.6%), while the lowest rate was observed among Hakka Taiwanese in the south of Taiwan (2.5%). In comparing with different ethnic groups, the highest prevalence was found among Fukien Taiwanese (8.1%) and the lowest among Mainland Chinese (4.9%). Among the different geographical areas, the highest positive rate was found in western Taiwan (7.1%) and the lowest in southern Taiwan (5.4%). Hantaan virus antibodies were also detected in 22 of 548 (4.0%) rat serum samples. The highest seropositive rate was found in rat sera collected from the Orchid Islets (21.4%). None of the rat sera collected from Hsinchu, Miaoli, Changhua, Nantu, Yunlin, Chiayi, Tainan, and Penghu Counties were positive. Hantaan virus antibodies were found in rats: *Rattus rattus* (20%), *Bandicota indica* (9.0%), *Rattus norvegicus* (8.3%), *Bandicota nemorivaga* (6.3%), *Rattus losea* (4.2%), and *Apodemus agrarius* (1.6%). Hantaan virus antibodies were not detected in rat sera collected from species of *Rattus coxinga, Rattus culturatus, Mus musculus, Mus caroli, Suncus murinus,* and *Apodemus semotus.* The results show that the Hantaan or Hantaan-related virus exists and is distributed widely in both human and rats in Taiwan.

KEY WORDS: seroprevalence, Hantaan virus, human, rat, geographical variation

INTRODUCTION

Hantavirus, a new genus of *Bunyaviridae* [Brown, 1989], can cause hemorrhagic fever with renal syndrome (HFRS) [Lee, 1982a,b; World Health Organization, 1983] and pulmonary syndrome [Centers for Disease Control, 1993; Duchin et al., 1994]. The clinical manifestations of diseases caused by hantavirus infection vary from mild to severe symptoms, with a mortality rate ranging from 5% to 60% [Lee and Van der Groen, 1989; Centers for Disease Control, 1994]. A prototype virus of hantavirus, Hantaan virus antigen was first demonstrated in the wild rodent, *Apodemus agrarius,* in 1976 [Lee and Lee, 1976], and similar agents were also isolated in 1978 from patients with Korean hemorrhagic fever [Lee et al., 1978]. Seroepidemiological studies have shown that hantavirus infection is found worldwide in humans and rats [LeDuce et al., 1984, 1985, 1986; Lee and Van der Groen, 1989; Yangihara, 1990; Nuti et al., 1992; Danes et al., 1992; Tantivanich et al., 1992; Niklasson et al., 1993; McKenna et al., 1994]. Most clinical cases of HFRS have been reported in Japan, Korea, China, Russia, Scandinavia, and Europe [Lee and Van der Groen, 1989; Niklasson, 1992]. Taiwan is located near southern China where hantavirus and its associated hemorrhagic fever diseases are endemic. It is therefore worthwhile to examine the prevalence of hantavirus infection in Taiwan. In a previous study, Hantaan virus antibodies were detected in 22% (6/27) of rat serum samples collected in Taiwan [LeDuce et al., 1986]. In LeDuce's study, the sample size was too small to determine the prevalence of Hantaan virus infections in rats throughout Taiwan. The prevalence

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in Taiwan has not been documented previously. In order to assess the prevalence of Hantaan virus infection in Taiwan, both human and rat sera were collected and tested for the presence of Hantaan virus antibodies.

MATERIALS AND METHODS

Sera Sample Collection

The general population of Taiwan was divided into 19 different strata according to ethnic characteristics and residential areas. Four ethnic groups were chosen: Aborigines, Fukien Taiwanese, Hakka Taiwanese, and Mainland Chinese whose parents were born in mainland China. Residential areas included northern, southern, western, and eastern Taiwan and the offshore islets of Orchid and Penghu. One urban or rural township or metropolitan precinct was randomly selected from each region. There was no Hakka Taiwanese group from the offshore islets. A total of 6,536 sera samples were collected and used for testing. An additional 548 sera samples collected from wild rats by blood sampling paper (Toyo Roshi Kaisha, Tokyo, Japan) and 74 serum samples collected from patients with renal syndrome were also included in this study.

Virus Antigen Preparation

Vero E6 cells growing in the 75-cm^2 tissue culture flasks were infected with Hantaan virus 76–118. Following incubation for 7 days, the infected cells were harvested by trypsin dispersion and centrifugation. After that, the cells were suspended in phosphate-buffered saline with 2% fetal calf serum and spotted onto ten-well slides (Cel-Line, Newfield, NJ). After air drying, the infected cells were fixed with cold acetone for 10 min and used as the viral antigen for antibody determination. A similar preparation from uninfected Vero E6 cells was used as the control.

Indirect Immunofluorescent Antibody (IFA) Test

The IFA method described by Lee et al. [1978] was used for detection of Hantaan virus antibodies. Fluorescein-conjugated anti-human immunoglobulins (IgA + IgG + IgM) (Cappel, Westchester, PA) and anti-rat immunoglobulin (Dako, Glostrup, Denmark) were used in the study. The sera were examined dilutions of 1:16 (human sera) and 1:32 (rat sera). Each diluted serum sample was reacted with both the viral antigen slide and control antigen slide prepared as described above. The characteristic discrete granular cytoplasmic fluorescence stains, observed in viral-infected cells but not in control cells, were considered as positive reactions for Hantaan virus antibody.

RESULTS

Age- and sex-specific seropositive rates of Hantaan virus antibodies among 6,536 randomly selected subjects from the general population are shown in Table I. There were five female subjects whose age was not recorded. The overall Hantaan virus antibody seropositive rates for males and females were 6.1% and 6.2%, respectively. The gender difference in the seropositive rate was not statistically significant ($P > 0.05$). Although a slightly higher seropositive rate (8.6%) was found in adults aged 40 to 49 years old, the age-specific seropositive rates were also not significantly different. Table II illustrates seropositive rates among 19 groups stratified on the basis of ethnicity and location. The overall seropositive rate of Hantaan virus antibodies among the general population in Taiwan was found to be 6.2%. Fukien Taiwanese (8.1%) and Aborigines (6.9%) had higher seropositive rates than Hakka Taiwanese (5.4%) and Mainland Chinese (4.9%). The seropositive rates were higher along the western coast of Taiwan (7.1%) and the offshore islets (7.0%) and lower in northern (5.5%) and southern parts of Taiwan (5.4%). The ethnic differences in seropositive rates were not consistent from one geographical area to the next, and the geographical variations did not follow along ethnic lines.

TABLE I. Age- and Sex-Specific Seropositive Rates of Hantaan Virus Antibodies Among 6,536 Randomly Selected Study Subjects in Taiwan*

	Males		Females[a]	
Age in years	Tested No.	Seropositive No. (%)	Tested No.	Seropositive No. (%)
<10	325	23 (7.1)	258	22 (8.5)
10–19	573	41 (7.2)	571	34 (6.0)
20–29	395	20 (5.1)	618	28 (4.5)
30–39	445	17 (3.8)	584	36 (6.2)
40–49	337	30 (8.9)	455	38 (8.4)
50–59	485	21 (4.3)	441	31 (7.0)
60–69	464	29 (6.3)	301	13 (4.3)
>69	158	13 (8.2)	121	7 (5.8)
Total	3,182	194 (6.1)	3,349	209 (6.2)

*Antibody detected at 1:16 dilution of serum by immunofluorescence stain.
[a]Five female subjects without information on age were excluded.

The seropositive rates of Hantaan virus antibodies by residential status are shown in Table III. The lowest seropositive rate was found in urban areas (5.1%) and the highest on the offshore islets (7.0%), but the difference in seropositive rates among the four differential residential status was not statistically significant ($P > 0.05$).

Two of 74 serum samples collected from the patients with renal syndrome were seropositive for Hantaan virus antibodies. One of them showed a higher titre at 1:128 dilution, while another was only 1:16 dilution. Immunoglobulin G, A, and M antibodies against Hantaan virus in these two cases were also measured. Only IgG viral antibody was detected in both cases.

Hantaan virus antibody was detected in 22 of 548 (4.0%) rat serum samples collected in Taiwan (Table IV). The highest prevalence rate was found in rats caught on the Orchid Islets (21.4%). All of rat serum samples collected at Hsinchu, Miaoli, Changhua, Nantu, Yulin, Chiayi, Tainan, and Penghu Counties were seronegative for Hantaan virus antibody. A higher seropositive rate was found among rats in northern Taiwan and the

TABLE II. Seropositive Rates of Hantaan Virus Antibodies in Taiwan by 19 Ethnic-Residence Strata

Ethnic groups	Resident areas	Hantaan virus positive rate	
		Number tested	Seropositive No. (%)
Aborigines	Northern area	317	18 (5.7)
	Western area	392	33 (8.4)
	Southern area	372	19 (5.1)
	Eastern area	388	26 (6.7)
	Orchid Islets	122	14 (11.5)
	Subtotal	1,591	110 (6.9)
Fukien Taiwanese	Northern area	261	20 (7.7)
	Western area	338	25 (7.4)
	Southern area	402	36 (9.0)
	Eastern area	204	12 (5.9)
	Penghu Islets	121	14 (11.6)
	Subtotal	1,326	107 (8.1)
Hakka Taiwanese	Northern area	722	41 (5.7)
	Western area	404	24 (5.9)
	Southern area	275	7 (2.5)
	Eastern area	390	25 (6.4)
	Subtotal	1,791	97 (5.4)
Mainland Chinese	Northern area	343	12 (3.5)
	Western area	397	26 (6.5)
	Southern area	390	16 (4.1)
	Eastern area	366	23 (6.3)
	Penghu Islets	332	12 (3.6)
	Subtotal	1,828	89 (4.9)
Total	Northern area	1,643	91 (5.5)
	Western area	1,531	108 (7.1)
	Southern area	1,439	78 (5.4)
	Eastern area	1,348	86 (6.4)
	Offshore islets	575	40 (7.0)
	Grand total	6,536	403 (6.2)

TABLE III. Seropositive Rates of Hantaan Virus Antibodies by Residence Areas

Residential status	Number tested	Seropositive No. (%)
Urban townships	1,496	77 (5.1)
Rural townships	2,996	190 (6.3)
Aboriginal townships	1,469	96 (6.5)
Offshore islets	575	40 (7.0)
Total	6,536	403 (6.2)

offshore islets, while lower seropositive were observed in western, eastern, and southern Taiwan. The prevalence of Hantaan virus antibody in different species of rats is outlined in Table V. Hantaan virus antibody were found in the species *Rattus rattus* (20.0%), *Bandicota indica* (9.0%), *Rattus norvegicus* (8.3%), *Bandicota nemorivaga* (6.3%), *Rattus losea* (4.2%), and *Apodemus agrarius* (1.6%). No antibody wsa detected in *Rattus coxinga, Rattus culturatus, Mus musculus, Mus caroli, Suncus murinus* or *Apodemus semotus.*

DISCUSSION

The results of this study show that the Hantaan virus or Hantaan-related virus exists and is widely distributed in both humans and rats in Taiwan. There was no significant difference in age-specific seroprevalence of Hantaan virus antibodies among the general population. The same findings were also reported in Shandong, Anhui, and Fujian of China [Xiong et al., 1990; Chen and Hu, 1992; Zhang et al., 1993] and along the Nile river delta in Egypt [Corwin et al., 1993]. There was no significant difference in seroprevalence between males and females in this study. Similar observations were reported in Egypt [Corwin et al., 1992] and some tropical areas [Nuti and Lee, 1991].

Although Fukien Taiwanese and Aborigines had a higher seropositive rate than Hakka Taiwanese and Mainland Chinese, these ethnic differences were inconsistent from one geographical area to the next. Likewise seropositive rates were found to be higher in western Taiwan and the offshore islets, but these variations also did not correlate to the different ethnic groups. It seems reasonable to suggest that neither ethnicity nor residential area has any significant impact on the Hantaan virus prevalence in Taiwan. Seropositive rates of Hantaan virus antibodies were found to be lower in urban areas than in rural areas (Table III). This may suggest that the chance of being exposed to Hantaan virus is lower in urban areas than other areas.

The overall seropositive rate of Hantaan virus antibodies in Taiwan was 6.2%. This is comparable to the rate in some HFRS-endemic areas, including Korea [Lee, 1982a,b], China [Chen et al., 1986], and Russia [Tkachenko et al., 1982], and some HFRS-nonendemic areas including Egypt [Corwin et al., 1992], and central

TABLE IV. Seropositive Rates of Anti-Hantaan Virus Antibodies in Rat Serum Samples Collected in Taiwan by Geographical Area

Areas	Number tested	Seropositive No. (%)
Northern area		
Ilan	23	1 (4.3)
Taipei	40	6 (15.0)
Taoyuan	24	2 (8.3)
Hsinchu	39	0
Subtotal	126	9 (7.1)
Western area		
Miaoli	54	0
Taichung	17	1 (5.9)
Changhua	28	0
Nantu	10	0
Subtotal	109	1 (0.9)
Southern area		
Yunlin	26	0
Chiayi	8	0
Tainan	15	0
Kaosiung	34	2 (5.9)
Pintung	27	2 (7.4)
Subtotal	110	4 (3.6)
Eastern area		
Hualian	134	4 (3.0)
Taitung	25	1 (4.0)
Subtotal	159	5 (3.1)
Offshore islets		
Penghu	30	0
Orchid Islet	14	3 (21.4)
Subtotal	44	3 (6.8)
Total	548	22 (4.0)

TABLE V. Seropositive Rates of Anti-Hantaan Virus Antibodies in Different Species of Rat in Taiwan

Species	Number tested	Seropositive No. (%)
Rattus rattus	10	2 (20.0)
Rattus norvegicus	12	1 (8.3)
Rattus losea	212	9 (4.2)
Rattus coxinga	2	0
Rattus culturatus	1	0
Bandicota indica	11	1 (9.0)
Bandicota nemorivaga	127	8 (6.3)
Mus musculus	20	0
Mus caroli	14	0
Suncus murinus	70	0
Apodemus agrarius	63	1 (1.6)
Apodemus semotus	6	0
Total	548	22 (4.0)

African countries [Gonzalezet et al., 1989]; however, no clinical case of Hantaan virus infection has been officially documented in Taiwan. Only two patients with the renal syndrome were seropositive. One case was a 23-year-old woman. The patient had proteinuria, hematuria, and fever without rash. Blood urea nitrogen, uric acid, and creatinine were within the normal range. The Hantaan virus antibody level was 1:16. The other case was a 49-year-old woman. The patient had a fever at admission and proteinuria for 5 days. Blood urea nitrogen, uric acid, and creatinine were 40.9 mg/dL, 10.1 mg/dL, and 1.8 mg/dL, respectively. The Hantaan virus antibody level was 1:128. No virus-specific IgM antibody was found in these two cases. The etiological role of Hantaan virus in these two patients could not be concluded. The results of this study suggest that almost all hantavirus infections in Taiwan were clinically asymptomatic. Most positive serum samples had titers ranging from 1:16 to 1:32 (70.8%). The virus in Taiwan seems to be different antigenically from the prototype Hantaan virus. As there was a broad cross reaction for the IFA method used in this study, a more specific method such as plaque reduction neutralization may be required to solve this problem [LeDuce et al., 1984; 1985].

The serosurvey of wild rats indicated that the hantavirus infection in rats is widely distributed in Taiwan (Table IV). Although an increased seropositive rate was observed in some areas, the geographical variations were inconsistent. The highest seropositive rates for humans and rats were found on the Orchid Islets. Since too few rats were examined in this study, the significance of their serological findings need further investigation. There are at least eight distinct groups of hantaviruses that have been identified in rats throughout the world, based on serological and epidemiological relationships [Chu YK et al., 1994; Elliott et al., 1994; Xiao et al., 1994; Chizhikov et al., 1995]. These groups are represented by Hantaan virus, an *Apodemus agrarius* isolate; Seoul virus, a *Rattus norvegicus* isolate; Puumala virus, a *Clethrionomys glareolus* isolate; Prospect Hill virus, a *Microtus pennsylvanicus* isolate; Thailand virus, a *Bandicota indica* isolate; Dobrava virus, an *Apodemus flavicollis* isolate; Thottapalayam virus, a *Suncus murinus* isolate; and Sin Nombre virus, a *Peromyscus maniculatus* isolate. Seropositivity was most common in *Rattus rattus, Rattus norvegicus, Rattus losea, Bandicota indica,* and *Bandicota nemorivaga* in Taiwan. The predominant natural hosts identified in this study proved different from the findings in a number of Hantaan virus endemic areas where the major animal host was *Apodemus agrarius* [Lee and Van der Groen, 1989; Lee and Lee, 1978; Chen et al., 1986]. The antigenic cross-reactivity was found among Hantaan virus, Seoul virus, and Thailand virus [Chu et al., 1994]. Seropositive samples found in *Rattus* and *Bandicota* in Taiwan may be due to a cross reaction with Hantaan virus used in the study. To date, *Bandicota* have been found to carry only the Thailand virus, which has not been demonstrated to cause disease in humans. These findings strongly suggest that hantavirus infections in humans in Taiwan is predominantly caused by a Seoul virus–like agent. Some more specific methods such as neutralization assays for viral antibody determination are required to strengthen these findings. Hantavirus from rat in Taiwan should be isolated and characterized in the near future. A further characterization of the etiology of hantavirus accounting for human disease in Taiwan should be undertaken.

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